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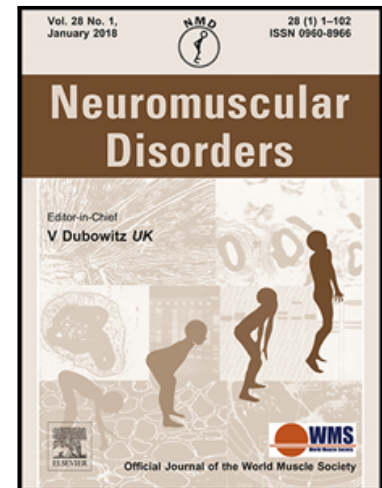
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## Accepted Manuscript

Functional impairments, fatigue and quality of life in RYR1-related myopathies: a questionnaire study

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**Highlights**

- RYR1-related myopathies are associated with functional impairments and chronic fatigue
- This accounts for congenital myopathies and to a lesser extent for malignant hyperthermia
- This results in substantial loss of quality of life

ACCEPTED MANUSCRIPT

# Functional impairments, fatigue and quality of life

## in *RYR1*-related myopathies: a questionnaire study

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**Abstract**

Mutations in *RYR1* are a common genetic cause of non-dystrophic neuromuscular disorders. To obtain baseline data concerning the prevalence of fatigue, the psychological disease burden and quality of life associated with these common conditions, we performed a questionnaire study. Seventy-two patients were included in this study, 33 with a congenital myopathy and 39 with malignant hyperthermia or exertional rhabdomyolysis. Our results showed that patients with *RYR1*-related myopathies have more functional impairments and significant chronic fatigue compared to healthy controls, with almost half of patients being severely fatigued. Whilst fatigue, pain and associated physical and social difficulties were more pronounced in those with permanent phenotypes, individuals with intermittent phenotypes also scored higher in all relevant categories compared to healthy controls. These findings indicate that *RYR1*-related myopathies, despite being often considered relatively mild conditions, are nevertheless associated with severe fatigue and functional limitations, resulting in substantial loss of quality of life. Moreover, milder but in essence similar findings in patients with *RYR1*-related malignant hyperthermia and rhabdomyolysis suggest that those phenotypes are not truly episodic but in fact associated with a substantial permanent disease burden. These preliminary data should help to design more comprehensive quality of life studies to inform standards of care.

## Introduction

Mutations in *RYR1*, the gene encoding the sarcoplasmic reticulum (SR) type 1 ryanodine receptor (RyR1), have emerged as the most common genetic cause of non-dystrophic neuromuscular disorders in recent years.[1] *RYR1* mutations give rise to a wide variety of myopathies presenting throughout life [2], ranging from early-onset congenital myopathies (for review, Jungbluth et al. [3]) to episodic manifestations in adulthood such as exertional rhabdomyolysis (RM), malignant hyperthermia during anesthesia with susceptibility proven by an in vitro contracture test (MH) and periodic paralysis [4] in otherwise healthy individuals. The very wide *RYR1*-associated clinical spectrum is due to the highly variable functional impact of *RYR1* mutations on the RyR1 receptor, the principal skeletal muscle calcium release channel with a crucial role in excitation-contraction coupling (ECC).

The weakness associated with early-onset *RYR1*-related congenital myopathies may be considerable and pose a substantial disease burden. Although fixed weakness is rare in episodic *RYR1*-associated RM and MH, individuals presenting with these features may nevertheless experience significant fatigue and myalgia in between episodes.[5] Myalgia may also be a prominent additional feature in early-onset *RYR1*-related myopathies such as central core disease (CCD), and has been reported in these conditions even before their genetic resolution.[6] Moreover, non-skeletal muscle manifestations, including an increased bleeding tendency and bowel and bladder symptoms due to smooth muscle dysfunction are increasingly recognized, and reflective of *RYR1* expression in tissues other than striated skeletal muscle.[2, 7-11] These complex disease phenotypes are likely to have a substantial impact on the quality of life (QoL) in affected individuals, yet no systematic studies investigating the associated fatigue, pain and functional impairments have been performed in *RYR1*-related disorders to date.

To obtain baseline data concerning the functional impairments, fatigue and QoL associated with these common conditions, we performed a questionnaire study focussing on these features in patients with *RYR1*-related myopathies throughout the recognized disease spectrum.[2] Standardized

questionnaires were used to obtain information on: functional impairments, fatigue, symptoms of psychopathology and other aspects of QoL. We compared patients with *RYR1*-related myopathies with healthy controls and with patients affected by a progressive neuromuscular disorder with multisystem involvement, MELAS (**M**itochondrial **E**ncephalomyopathy, **L**actic **A**cidosis, and **S**troke-like episodes,) spectrum disorder. In addition, within the group of patients with *RYR1*-related myopathies, the subgroup of patients with 'permanent phenotypes' (congenital myopathies) were compared to the patients with 'episodic phenotypes' (MH and RM).

The results of this explorative study will improve management of patients with *RYR1*-related myopathies, and enable the definition of areas in need of further research concerning the disease burden associated with these common neuromuscular disorders.

## Methods

### *Patients*

All patients with a genetically confirmed *RYR1*-related disorder seen at the Department of Neurology (Radboudumc) and the Dutch national referral centre for Malignant Hyperthermia (Canisius-Wilhelmina Hospital) in Nijmegen, The Netherlands, were approached to participate in this descriptive questionnaire study. Additional patients were approached through the Dutch national patient organization for myopathies ([www.spierziekten.nl](http://www.spierziekten.nl)) as well as Dutch neuromuscular neurologists ([www.spierziektencentrum.nl](http://www.spierziektencentrum.nl)). This resulted in a total of 200 patients being invited through a dedicated invitation letter sent to their home addresses. The key neuromuscular features of a proportion of these patients have already been reported by Snoeck et al.[2]

### *Methods*

This study was approved by the regional Ethics Committee: Human Research Committee region Arnhem and Nijmegen (CMO 2016-2954). All participants gave written informed consent.

After informed consent, patients received an email with a link, which led to the questionnaire in a private and secure environment (Radquest 2.0). The patients were asked to open this link and fill in the questionnaires at their preferred place and time. Once commenced, the questionnaire had to be completed within 24 hours to prevent errors in data storage. If the questionnaire was not completed within two weeks, patients received a reminder email. If this neither resulted in completion, a reminder phone call followed after a further two weeks.

### *Questionnaires*

Various aspects of functional impairments, fatigue and QoL were assessed with questionnaires that have been used before and validated in neuromuscular disorders.[12, 13]

*Functional impairment* was assessed using the Sickness Impact Profile (SIP), aimed at assessing changes in everyday activities due to sickness and covering the following dimensions of functioning: sleep/rest (7 items); home management (10 items); mobility (addressing the ability to move indoors and outdoors; 10 items); social interactions (20 items); ambulation (addressing the ability to walk and walk stairs, and use of walking aids; 12 items); alertness behaviour (10 items); work (3 items); and recreation (8 items).[14, 15] Higher scores reflect more impairment. Scores were compared to a group of 83 healthy subjects.[16]

*Fatigue severity* was assessed with the Checklist Individual Strength (CIS). The CIS is a questionnaire with twenty items and the following four subscales: perceived fatigue severity (8 items), concentration (5 items), motivation (4 items) and physical activity (3 items). The total score is calculated by adding up the scores for each subscale (range = 20-140), with higher scores indicative of a higher disease burden.[17] A CIS-fatigue score of 35 or more was used to identify severe fatigue. A representative sample from the Dutch general population was used as a reference group.[18]



*Symptoms of psychopathology* were assessed by the SCL-90. This questionnaire consists of 90 descriptions of complaints on several subscales (agoraphobia, anxiety, depression, somatisation, obsessive-compulsive behaviour, interpersonal sensitivity, hostility, sleep). The statements are rated on a five-point Likert scale (a psychometric scale commonly involved in questionnaire research with scores 1-5; 1: strongly disagree; 2: disagree; 3: neither agree nor disagree; 4: agree; 5: strongly agree)[19] Higher scores reflect more symptoms of psychopathology. A total SCL-90 score of more than 160 is indicative of high psychological distress, while a score of more than 200 is indicative of a psychiatric disorder.[20, 21]

For additional assessment of anxiety and depression the Hospital Anxiety and Depression Scale (HADS), specially developed for the assessment in a hospital population, was used. The HADS includes seven items about depression and seven items about anxiety. Its total score can be used as a measure of general distress. Total scores  $\geq 11$  are indicative of high distress.[22] [23] The HADS is designed to assess symptoms of depression in people with medical conditions by controlling for vital aspects of depression that could easily interfere with symptoms of the disease.

Overall *quality of life* was assessed using the RAND-SF36 questionnaire. Subscales investigated several dimensions of QoL (physical functioning, social functioning, emotional functioning, general health status, perceived change in health status, mental health, vitality and pain). Scores range from 0 (maximum limitations) to 100 (optimal functioning).[24] A commonly used representative sample of the Dutch general population (men and women aged 18 to 75 years) was used as a reference group.[25]

Statistics. Data analysis was performed using SPSS (version 22). Descriptive statistics were used to describe the characteristics of the sample as well as patient reported outcomes on functional impairment, fatigue, psychological symptoms, and QoL. Fisher exact test was used to compare the response and non-response group (age, sex and phenotype). One-sample t tests were used for the

comparison of *RYR1*-mutated patients with healthy controls, and a sample of patients with a MELAS spectrum disorder.[13] ANOVA's were used to compare permanent with episodic *RYR1*-related phenotypes with regards to patient reported outcomes concerning QoL, functional impairment, symptoms of psychopathology, and fatigue. Because of the large number of variables to explore and comparisons to make, and its increased risk of Type 1 errors, Bonferroni adjustments to the alpha level were applied (statistical significance Rand-sf36  $p<.006$ ; SIP  $p<.006$ ; SCL90  $p<.006$ ; HADS  $p<.017$ ; CIS  $p<.013$ ).

## Results

### *Response*

In total 200 invitation letters were sent. Sixty-one patients did not respond after sending two letters and could not be reached by phone on two subsequent attempts. Hence, we managed to contact 139 patients, of which 26 patients responded that they were not willing to participate in this study, and 113 patients agreed to participate. Of these 113 patients, 94 responded with an email address and a consent form (13 of whom did not return their consent form; six did not send an email address; See Figure 1). 72 Questionnaires were completed, resulting in a response rate of 52% of the patients who were initially contacted (72 of 139), and 77% of the patients who initially responded positively to our invitation (72 of 94). Demographic and clinical characteristics of the patients are summarized in Table 1. No differences between response group ( $n=72$ ) and non-response group ( $n=67$ ) could be identified based on demographic characteristics (age and sex). Among the non-responders were more patients with an episodic phenotype: 48 of 67 versus 39 of 72 in the response group ( $p=0.04$ ).

The clinic-pathological diagnoses are summarized in table 1. Among the patients with a permanent phenotype ( $n=33$ ) were 18 with CCD, three with Multi-minicore Disease (MmD), two with Centronuclear Myopathy (CNM), two with King-Denborough syndrome (KDS), two with Congenital Fibre Type Disproportion (CFTD), three with an axial myopathy, and three with a congenital

myopathy not otherwise specified. The episodic phenotype group (n=39) included 37 patients with MH, one with ERM, and one with hyperCKemia.

#### *Functional impairment (SIP)*

Functional impairment as assessed with the eight dimensions of the Sickness Impact Profile (SIP) is shown in Table 2. Mean scores on all dimensions reflected more functional impairments in patients with *RYR1*-related myopathies compared to healthy controls (*t* values varied from 3.020 (mobility:  $p=.004$ ) to 6.277 (ambulation:  $p<.001$ ), except for work ( $t(71)=2.417$ ,  $p=.018$ ). Compared to MELAS spectrum disorder patients, *RYR1*-mutated patients showed less impairment in mobility ( $t(71)=-3.522$ ,  $p=.001$ ), social interaction ( $t(71)=-3.870$ ,  $p<.001$ ), alertness behavior ( $t(71)=-6.392$ ,  $p<.001$ ) and recreation ( $t(71)=-3.489$ ,  $p=.001$ ).

#### *Fatigue (CIS)*

On the four subscales of the CIS and its total score, *RYR1*-mutated patients scored significantly higher than healthy controls (*t* values varied from 3.265 (concentration:  $p=.002$ ) to 9.201 (fatigue:  $p<.001$ ), Table 2. Scores were significantly lower than MELAS spectrum disorder patients. Severe levels of fatigue (CIS fatigue > 35) were reported by 46% of the patients (n=33) compared to 60% in MELAS spectrum disorder patients.

#### *Symptoms of psychopathology (SCL-90)*

Scores on the eight subscales of the SCL-90 revealed significant more problems compared to healthy controls on somatisation ( $t(71)=.038$ ,  $p<.001$ ). Results are summarized in Table 2. On the (total score of the) SCL-90, 13% of patients scored above the cut-off for high psychological distress.

#### *Mental functioning (HADS)*

In general, patients showed no difference in levels of depression compared to MELAS spectrum disorder patients ( $t(71)=-.986$ ,  $p=.327$ ) or healthy Dutch controls ( $t(71)=2.166$ ,  $p=.034$ ). Scores on anxiety were better than those of the control group ( $t(71)=-2.740$ ,  $p=.008$ ) and the MELAS spectrum disorder patients ( $t(71)=-3.238$ ,  $p=.002$ ). General distress was similar to healthy controls ( $t(71)=.039$ ,  $p=.969$ ) and better than the MELAS spectrum disorder patients ( $t(71)=-2.389$ ,  $p=.020$ ) (Table 2).

Looking at subgroups scoring above the cut-off, results on the HADS indicated that 21% and 17% of the patients experienced clinically relevant symptoms of, respectively, depression and anxiety. One third of the patients (33%) scored above the cut-off of clinical relevant levels of general distress.

#### *Quality of life (RAND36)*

Results from the QoL questionnaire study in *RYR1*-mutated patients are presented in Table 2. Compared to a control group of healthy individuals, *RYR1*-mutated patients show impairment in almost all QoL domains ( $t$  values varied from  $-5.877$  (physical functioning:  $p<.001$ ) to  $-3.142$  (experienced health change:  $p=.002$ ) except for emotional role functioning ( $t(71)=-.199$ ,  $p=.843$ ), and mental health ( $t(71)=.278$ ,  $p=.782$ ) and pain ( $t(71)=-2.740$ ,  $p=.008$ ). In comparison with a sample of patients with a mitochondrial disease (MELAS spectrum disorder), *RYR1*-mutated patients experience a better QoL ( $t$  values varied from  $3.356$  (physical role functioning:  $p=.001$ ) to  $6.048$  (general health:  $p<.001$ ) except for equally impaired scores on physical functioning ( $t(71)=-.664$ ,  $p=.509$ ), pain ( $t(71)=.945$ ,  $p=.348$ ), and experienced health change ( $t(71)=.531$ ,  $p=.597$ ).

#### *Comparison of permanent and episodic phenotypes*

Of 72 *RYR1*-mutated patients, 33 patients had a permanent and 39 had an episodic phenotype. The permanent phenotype group experienced worse physical functioning ( $F(1,70)=44.6$ ,  $p<.001$ ), and more functioning impairments in home management ( $F(1,70)=9.8$ ,  $p=.003$ ), mobility ( $F(1,70)=7.3$ ,  $p=.009$ ), and ambulation ( $F(1,70)=39.9$ ,  $p<.001$ ). With regards to psychological functioning and fatigue, no differences between the groups were found.

Regarding QoL, compared to healthy controls patients with a permanent phenotype experienced lower physical (role) and social functioning, less vitality, more pain, worse general health and experienced health change. Regarding functional impairment, they experienced more difficulties in sleep/rest, home management, mobility, social interaction, ambulation, recreation. Furthermore, with regards to psychological functioning, these patients reported more somatisation. With regards to fatigue, patients reported more perceived fatigue, motivation and activity problems (t-values varied from 2.906 (mobility:  $p=.006$ ) to -10.019 (physical functioning:  $p<.001$ ). Anxiety levels were significantly lower than those of healthy controls ( $t=-4.126$ ;  $p<.001$ ).

Patients with an episodic phenotype reported more perceived fatigue severity and motivation problems, more difficulties in social interaction, and more impairment in recreation and pastimes (t values varied from 3.206 (recreation:  $p=.003$ ) to 5.447 (fatigue:  $p<.001$ ) compared to healthy controls. Inspection of single items revealed that these patients report decreased sexual activity, took it slower with some of their usual activities, went out for entertainment less often, enjoyed less recreational activities, and dedicated themselves to hobbies for shorter periods of time.

## Discussion

The present questionnaire-based study to our knowledge is the first study to systematically investigate the impact of *RYR1*-related myopathies in affected individuals, ranging from functional impairments and fatigue to psychological wellbeing and QoL in general. Our study showed that patients with *RYR1*-related myopathies throughout the recognized disease spectrum have more functional impairments and experienced chronic fatigue compared to healthy controls, with almost half of all patients being severely fatigued (CIS fatigue > 35). Whilst functional impairments and fatigue were more pronounced in those with congenital myopathy phenotypes, individuals with episodic phenotypes also scored higher in all relevant categories compared to healthy controls, but less compared to a multisystem disorder with neuromuscular involvement, MELAS. Although one

third (33%) of patients scored above the cut-off point for high distress, in general scores indicative of psychological functioning were similar compared to the normal control population.

Findings of increased fatigue as well as impaired physical and social functioning are not unexpected in *RYR1*-related congenital myopathies (permanent phenotypes), considering the associated variable but often substantial weakness. However, the severity of the associated disease burden suggested by our study is noteworthy, considering that *RYR1*-related myopathies are often regarded as relatively mild conditions compared to other congenital myopathies. These findings are even more remarkable as our cohort included only adult patients, thus excluding some of the early-onset *RYR1*-related paediatric manifestations associated with even more profound weakness and disability. Our study also indicates specific areas of malfunctioning in individuals with *RYR1*-related disorders that might warrant further in-depth exploration, certain aspects of social interaction (such as decreased sexual activity), recreational activities (for example, performing such activities more slowly) and general problems with motivation.

Milder but essentially similar findings in individuals with *RYR1*-related MH and RM suggest that these conditions are not purely episodic conditions, but do have a phenotype associated with a substantial disease burden also between episodes. The concept of *RYR1*-related RM exhibiting also inter-episodic myopathic features is supported by the additional presence of (exertional) myalgia without demonstrable muscle breakdown in individuals with *RYR1*-related RM and their carrier relatives, initially reported by our group [5] and independently confirmed in subsequent smaller cohorts from Denmark and South America.[26, 27] One of these series also already suggested an effect on activities of daily living in patients with *RYR1*-related RM, something which has more systematically been explored in the present study, also with regards to its impact on QoL parameters. Parameters of physical and social functioning as well as QoL in individuals with *RYR1*-related MH, representing almost all patients with episodic phenotypes in our cohort, are here reported for the first time: these parameters suggest that as in patients with *RYR1*-related RM, patients with *RYR1*-related MH do also have a substantial disease burden in daily life, a concept that is currently not well-established.

Although no systematic studies have been performed yet, earlier observations in isolated families with *RYR1*-related MH suggest a high prevalence of pain, in particular affecting the lower back muscles [28], a muscle group that may also become manifestly weak over time in such patients.[29] Taken together, these observations emphasize the previous notion that *RYR1*-related MH and RM are different but closely related clinical manifestations of the same mutational spectrum, presenting predominantly episodically on triggering but associated with a substantial permanent disease burden in daily life.

Although no detailed QoL studies have been reported in *RYR1*-related and other congenital myopathies to date, similar studies have been performed in other, mainly dystrophic neuromuscular disorders such as Duchenne muscular dystrophy, myotonic dystrophy type 1 (DM1) and facioscapulohumeral muscular dystrophy (FSHD), but also neurogenic conditions such as spinal muscular atrophy.[30-33] These studies may serve as a point of comparison for the present study but may also help to delineate specific determinants of impaired QoL in neuromuscular disorders. In particular, comparison with previously reported cohorts of FSHD (n=139), DM1 (n=322), and hereditary motor and sensory neuropathy type I (HMSN; n=137) from our centre showed a lower prevalence of severe fatigue (CIS fatigue $\geq$ 35) in patients with *RYR1*-related myopathies (46% vs 61%, 74% and 64% respectively;  $p=0.04$ ;  $p,0.0001$ ;  $p=0.01$  respectively).[34] In this previous study, regression analyses were carried out to determine the contribution of different dimensions to fatigue severity.[34] The number of patients in our current study was too small to perform a similar analysis, however, this ought to be considered in larger prospective studies in future concerning *RYR1*-related and other congenital myopathies.

Impairment of physical activity and muscle strength, important contributors to altered QoL in conditions such as FSHD and DM1 [35], are likely to have contributed to impaired QoL in *RYR1*-related congenital myopathies (permanent phenotypes) but are unlikely to explain similar observations in *RYR1*-related RM and MH, considering that individuals with these episodic phenotypes are normally strong (or even particularly athletic). It is conceivable that the absence of

weakness in combination with a large muscle mass in some of these individuals may enable them to participate effectively in strenuous sports (personal observation), an ability that in turn might predispose to a higher incidence of ERM, muscle fatigue and an adverse effect on QoL. The common occurrence of high levels of physical fitness and reduced exercise tolerance or lower fatigue thresholds in some individuals with *RYR1*-related episodic phenotypes may reflect specific effects of the dominant *RYR1* gain-of-function mutations typically underlying such phenotypes. Although not the focus of the present study, such mechanisms warrant further investigation in future, and may include (i) fatigue caused by continuous stimulation of SERCA activity indirectly mediated through a “leaky” RyR1 channel; (ii) high circulating levels of IL-6 in *RYR1* mutation carriers causing chronic pain both at rest and during activity [36, 37]; and (iii) fear of (recurrence of) rhabdomyolysis limiting the motivation to exercise in some patients. From a practical point of view, it is noteworthy that the substantial disease burden caused by exertional myalgia and fatigue may not be immediately obvious in patients with *RYR1*-related MH, considering their lack of weakness and often athletic muscle build; this is something that ought to be considered.[38, 39] Therefore, counseling of these patients should extend beyond prevention of recurrent MH or RM episodes, and include rehabilitation focused on pain and fatigue.

Considering that *RYR1*-related myopathies may show some multisystem features, we also compared *RYR1*-mutated patients with patients affected by MELAS, a mitochondrial multisystem disorder with muscle and brain features. In comparison to MELAS, *RYR1*-mutated patients generally have a better QoL, less functional impairment, less anxiety, less perceived fatigue, and are less often severely fatigued. This is not unexpected, considering that MELAS is a more extensive condition. A better example for comparison appears McArdle disease, another neuromuscular disorder with an often severe episodic phenotype that however has substantial permanent features, as evidenced by a recent questionnaire study including 81 patients, demonstrating lower clinical scores compared to the general population in physical domains of health-related QoL parameters.[40]



The main limitation of this study relates to the low response rate of 52% of patients who were invited to participate (or 77% of patients who had initially agreed to participate after having been invited), suggesting a potential selection bias. Although there were no differences in age and sex between the response and non-response group, the non-response group consisted of more patients with the episodic phenotype than the response group, suggesting that our results may be more reflective of the latter. In addition and non-regarding specific subgroups, more symptomatic patients may be more inclined to participate in such a symptom-centred questionnaire study, thus potentially leading to an overestimation of the severity of the associated disease phenotype. As a result of the cross-sectional questionnaire study design, we could not identify the causes of functional impairments and loss of QoL. Based on the limitations as outlined, more extensive prospective longitudinal studies focussing on *RYR1*-related myopathies will be required.

In conclusion, the present study demonstrates that both permanent and episodic *RYR1*-related disorders are associated with a substantial disease burden, characterized by functional limitations and severe fatigue, and a resulting loss of QoL. As such, our study challenges the concept of *RYR1*-related myopathies as relatively mild conditions, and of *RYR1*-related RM and MH as episodic conditions with no significant inter-episodic phenotypes. This study should provide the basis for more extensive studies investigating QoL in *RYR1*-related and other congenital myopathies, and alert physicians and multidisciplinary team members to the multiple and often hidden needs of patients presenting with *RYR1*-related RM and MH.

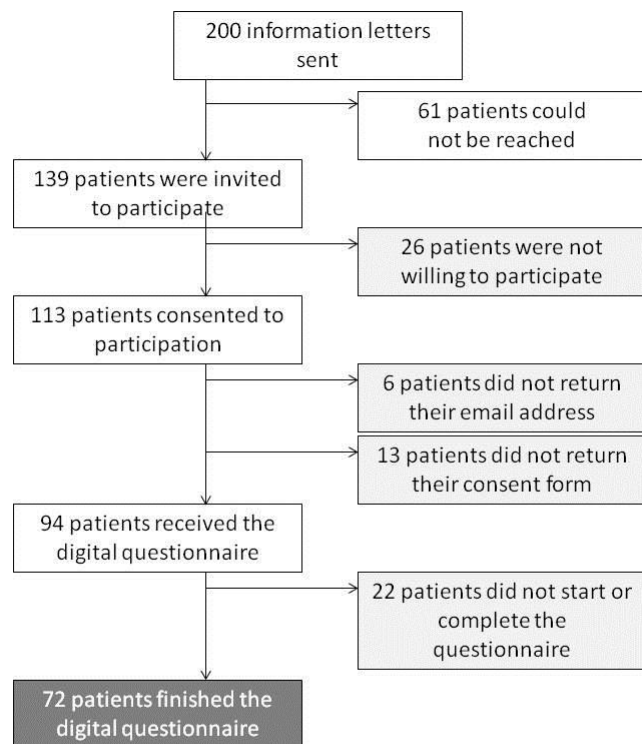
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**Figure 1: 1** Flowchart showing responses of patients

Non-response group in light grey boxes on the right; response group in dark grey box.



**Table 1. Patient characteristics**

Number and demographics of patients who participated in this questionnaire study. The number of patients are indicated for each phenotype. Patients were divided into i) a group with permanent weakness (n=33); i.e. the congenital myopathies and axial myopathy, and ii) a group with episodic symptoms provoked by anaesthesia, exertion or other triggers (n=39).

	<b>Total</b>	<b>Permanent phenotypes</b>	<b>Episodic phenotypes</b>
<b>Number of patients</b>	72	33	39
<b>Gender: Male</b>	37	18	19
<b>Age: Mean (SD)</b>	49.3 (14.2)	50.9 (14.6)	48.1 (13.9)
<b>Phenotype (N)</b>	CCD: 18	CCD: 18	
	MmD: 3	MmD: 3	
	CNM: 2	CNM: 2	
	KDS: 2	KDS: 2	
	CM: 3	CM: 3	
	Axial myopathy: 3	Axial myopathy: 3	
	CFTD: 2	CFTD: 2	
	MH: 37		MH: 37
	RM: 1		ERM: 1
	HyperCKemia: 1		HyperCKemia: 1

MH: Susceptible for malignant hyperthermia; RM: Exertional rhabdomyolysis; CCD: Central Core Disease; MmD: Multi-mincore Disease; CNM: Centronuclear Myopathy; KDS: King Denborough syndrome; CM: Congenital myopathy; CFTD: Congenital Fibre Type Disproportion.

**Table 2. Results of questionnaires in RYR1-related myopathies and MELAS**

Scores from patient-reported outcome measures in RYR1-related myopathy patients compared to patients with MELAS spectrum disorder and control subjects from the general population, based on specific questionnaires with separate domains.

Questionnaires / Domain	Mean (SD) of patients with RYR1-related myopathies n = 72	Mean (SD) of patients with MELAS spectrum disorder n = 72 [13]	Mean (SD) of control subjects in general population
<i>Functional impairment (SIP)</i>			
Sleep / Rest	44.8 (62.1) <sup>c</sup>	50.6 (52.9)	11.4 (26.0)
Home management	77.9 (97.6) <sup>c</sup>	86.9 (86.5)	8.8 (32.0)
Mobility	19.0 (49.3) <sup>b,c</sup>	39.5 (93.3)	1.5 (8.7)
Social interaction	75.8 (107.2) <sup>b,c</sup>	124.7 (142.0)	9.0 (26.9)
Ambulation	78.3 (105.9) <sup>c</sup>	59.9 (90.6)	0.0 (0.0)
Alertness behaviour	53.6 (97.6) <sup>b,c</sup>	127.1 (157.5)	15.4 (78.8)
Work	27.2 (50.7)	30.9 (59.1)	12.7 (64.4)
Recreation	49.7 (65.2) <sup>b,c</sup>	76.5 (71.7)	6.7 (21.7)
<i>Fatigue (CIS)</i>			
Perceived fatigue	31.7 (13.2) <sup>b,c</sup>	37.4 (12.8)	17.3 (10.1)
Concentration	12.0 (6.6) <sup>b,c</sup>	18.7 (9.2)	9.5 (5.9)
Motivation	12.3 (5.6) <sup>b,c</sup>	14.8 (6.3)	7.9 (4.1)
Activity	9.1 (5.3) <sup>b,c</sup>	11.9 (6.0)	6.6 (4.5)
<i>Symptoms of psychopathology (SCL90)</i>			
Agoraphobia	8.4 (3.2)		7.8 (1.5)
Anxiety	12.7 (4.1)		12.5 (3.1)
Depression	22.5 (8.3) <sup>c</sup>		20.4 (4.7)
Somatisation	19.5 (6.7) <sup>c</sup>		16.3 (4.0)
Obsessive-compulsive beh.	14.1 (5.3) <sup>c</sup>		12.7 (3.3)
Interpersonal sensitivity	23.0 (6.1)		23.3 (4.8)
Hostility	6.8 (1.3)		7.0 (1.2)
Sleep	5.6 (2.6) <sup>c</sup>		4.8 (1.9)
Total	123.53 (32.5)		
<i>Mental functioning (HADS)</i>			
Depression	4.4 (4.0)	4.9 (4.2)	3.4 (3.3)
Anxiety	4.0 (3.4) <sup>b,c</sup>	5.3 (4.2)	5.1 (3.6)
Total – General distress	8.4 (6.6)	10.3 (7.7)	8.4 (6.3)
<i>Quality of life (RAND36)</i>			
Physical functioning <sup>a</sup>	61.0 (30.1) <sup>c</sup>	63.4 (26.7)	81.9 (23.2)
Social functioning	76.6 (25.2) <sup>b,c</sup>	64.1 (24.3)	86.9 (20.5)
Physical role functioning <sup>a</sup>	56.9 (43.9) <sup>b,c</sup>	39.6 (42.5)	79.4 (35.5)

Emotional role functioning	83.3 (33.1) <sup>b</sup>	69.4 (40.2)	84.1 (32.3)
Mental health	77.3 (14.6) <sup>b</sup>	70.8 (17.6)	76.8 (18.4)
Vitality	57.9 (18.6) <sup>b,c</sup>	49.0 (18.8)	67.4 (19.9)
Pain	71.2 (25.8)	68.3 (25.9)	79.5 (25.6)
General health	60.1 (22.5) <sup>b,c</sup>	44.1 (22.4)	72.7 (22.7)
Experiences health change	44.4 (21.5) <sup>c</sup>	43.1 (21.1)	52.4 (19.4)

<sup>a</sup> items in the physical functioning domain address essential abilities of getting about in daily life (walking, walking up stairs, carry shopping bags, personal hygiene and getting dressed), whereas physical role functioning focuses on the difficulties in daily life due to impaired physical functioning (difficulties in working or fulfilling household duties);

<sup>b</sup> significant difference between *RYR1*-related myopathy patients and patients with MELAS spectrum disorder;

<sup>c</sup> significant difference between *RYR1*-related myopathy patients and control subjects from the general population.

**Table 3. Table 2. Results of questionnaires in permanent and episodic phenotypes of RYR1-related myopathies**

Scores from patient-reported outcome measures in patients with the the permanent phenotype compared to patients with the intermittent phenotype, and compared to control subjects from the general population

Questionnaires / Domain	Mean (SD) Permanent phenotype n = 33	Mean (SD) Episodic phenotype n = 39	Mean (SD) of control subjects in general population
<i>Functional impairment (SIP)</i>			
Sleep / Rest	51.2 (60.6) <sup>c</sup>	39.4 (63.6)	11.4 (26.0)
Home management	114.9 (99.7) <sup>b,c</sup>	46.6 (85.1)	8.8 (32.0)
Mobility	35.4 (66.9) <sup>b,c</sup>	5.2 (18.4)	1.5 (8.7)
Social interaction	93.0 (121.2) <sup>c</sup>	61.3 (92.9) <sup>c</sup>	9.0 (26.9)
Ambulation	147.2 (111.8) <sup>b,c</sup>	20.1 (53.1)	0.0 (0.0)
Alertness behaviour	45.6 (71.1)	60.3 (116.0)	15.4 (78.8)
Work	34.8 (62.9)	20.7 (37.2)	12.7 (64.4)
Recreation	61.2 (64.9) <sup>c</sup>	39.9 (64.8) <sup>c</sup>	6.7 (21.7)
<i>Fatigue (CIS)</i>			
Perceived fatigue	34.4 (12.2) <sup>c</sup>	29.3 (13.8) <sup>c</sup>	17.3 (10.1)
Concentration	11.7 (5.8)	12.3 (7.2)	9.5 (5.9)
Motivation	12.5 (5.5) <sup>c</sup>	12.2 (5.8) <sup>c</sup>	7.9 (4.1)
Activity	10.2 (5.3) <sup>c</sup>	8.1 (5.0)	6.6 (4.5)
<i>Symptoms of psychopathology (SCL90)</i>			
Agoraphobia	8.4 (2.9)	8.4 (3.4)	7.8 (1.5)
Anxiety	11.9 (2.4)	13.3 (5.1)	12.5 (3.1)
Depression	23.3 (8.6)	21.9 (8.1)	20.4 (4.7)
Somatisation	20.0 (6.6) <sup>c</sup>	19.0 (6.9)	16.3 (4.0)
Obsessive-compulsive behaviour	14.2 (4.2)	14.0 (6.2)	12.7 (3.3)
Interpersonal sensitivity	23.6 (6.3)	22.6 (5.9)	23.3 (4.8)
Hostility	6.6 (1.0)	6.9 (1.5)	7.0 (1.2)
Sleep	5.6 (2.3)	5.7 (2.9)	4.8 (1.9)
Total	124.5 (29.4)	122.7 (35.4)	
<i>Mental functioning (HADS)</i>			
Depression	4.6 (4.3)	4.3 (3.9)	3.4 (3.3)
Anxiety	3.2 (2.6) <sup>c</sup>	4.6 (3.9)	5.1 (3.6)
Total – General distress	7.8 (6.3)	8.9 (6.9)	8.4 (6.3)
<i>Quality of life (RAND36)</i>			
Physical functioning <sup>a</sup>	40.8 (23.6) <sup>b,c</sup>	78.2 (23.8)	81.9 (23.2)



Social functioning	73.1 (25.2) <sup>c</sup>	79.5 (25.1)	86.9 (20.5)
Physical role functioning <sup>a</sup>	49.2 (43.1) <sup>c</sup>	63.5 (44.0)	79.4 (35.5)
Emotional role functioning	80.8 (33.4)	85.5 (33.1)	84.1 (32.3)
Mental health	79.5 (13.3)	75.4 (15.5)	76.8 (18.4)
Vitality	55.3 (20.8) <sup>c</sup>	60.0 (16.5)	67.4 (19.9)
Pain	63.9 (24.6) <sup>c</sup>	77.3 (25.5)	79.5 (25.6)
General health	55.9 (21.2) <sup>c</sup>	63.7 (23.2)	72.7 (22.7)
Experienced health change	39.4 (18.8) <sup>c</sup>	48.7 (22.9)	52.4 (19.4)

<sup>a</sup> items in the physical functioning domain address the essential abilities of getting about in daily life (walking, walking upstairs, carry shopping bags, personal hygiene and getting dressed), whereas physical role functioning focuses on the difficulties in daily life due to impaired physical functioning (difficulties in working or fulfilling household duties);

<sup>b</sup> significant difference between *RYR1*-related myopathy patients and patients with MELAS spectrum disorder;

<sup>c</sup> significant difference between *RYR1*-related myopathy patients and control subjects from the general population.